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ORIGINAL ARTICLE

Management of T1G3 Transitional Cell Carcinoma of Urinary Bladder with Intravesical Bacillus Calmette-Guerin (BCG): Our Experience

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ABSTRACT

Aim: To determine efficacy of BCG in T1G3 urinary bladder tumors at department of urology Chandka Medical College Larkana.
Patients and Methods: This is retrospective study, patient were selected from hospital record from July 2016 to June 2022. Around 80 included in our study group who were treated in our department for management of high grade non-muscle invasive bladder tumor**.** After following inclusion and exclusion criteria TURBT were performed and BCG was installed intravesically for induction and maintenance purpose. Patients were followed for 5 years and data was collected on study specific proforma.
Results: 80 patients were included in our study with mean age 35year +5.5 SD. Transurethral resection of urinary bladder tumor was performed in all patients with bladder growth. Induction and maintenance instillation of bacillus Calmette-Guerin (BCG) therapy was given to all. The recurrence was noted in 5 patients (6.25%) and the progression was also seen in these 5 patients (6.25%). Disease-specific survival is 93.75% at the follow-up of 5 years. As prevalence of ca bladder is increasing day by day and bladder is sole organ for storing urine so nowadays strategies of treatment is bladder saving surgery. So patient will feel comfortable with natural bladder and on other hand it will minimize complication related to artificially generated urinary bladder.
Conclusion: Maintenance BCG therapy for T1G3 bladder tumors is an effective treatment, with satisfactory results and bladder preservation.
Keywords: Ca bladder, intravesival chemotherapy, BCG, T1G3 and management.

INTRODUCTION

The most common malignancy of the urothelial tract is urinary bladder tumor. Males are more commonly affected than females. Mostly urinary bladder tumors are epithelial in origin and most common type is transitional cell carcinomas, seen in 90% of patients. Second common variant is Squamous cell carcinomas, seen in 5% to 10% and third is adenocarcinomas, seen in 2%[1]. The prognostic factors for urinary bladder tumor are disease extent at time of diagnosis, histologic type and growth pattern of tumor. Most common presentation is with superficial disease. For superficial tumors diagnosis is made with resection of urinary bladder tumor and multiple biopsies with cystoscope and if needed mitomycin and BCG intravesically depending upon stage of NMIBC[1,2]. BCG is the gold standard treatment for intermediate and high-risk NMIBC since more than 50 years. Its role as a bladder preserving treatment isby delaying recurrence and preventing progression disease.[3]

It works through two mechanisms, (1) "Direct tumor response" (2) "immune response.", BCG attaches to urothelial cells through fibronectin and travels inside of bladder cancers cell through micropinocytosis and causes cell death by apoptosis or necrosis. Bladder cancer cells activate the immune system by upregulating antigen-presenting cells (major histocompatibility complex-II and intercellular adhesion molecule-1) and are presented to CD4 T cells.[4]

Current AUA and EAU guidelines on NMIBC recommend an induction course of BCG for high-risk disease. This is followed by one to three years of maintenance BCG treatment for BCG-responsive disease. For relapsed disease after BCG treatment, guideline recommendations for intermediate and high-risk categories disease include the institution of a second induction BCG course, citing evidence showing that approximately 50% of patients with recurrent NMIBC respond to a second induction course[3,4]Cystoscopy is ideal for diagnosis, staging, and definitive therapy of urinary bladder tumor. Staging of tumor with imaging helps to differentiate superficial tumors from deep invasive tumors. Staging accuracies for bladder carcinoma with CT scan is (40% to 92%) and with MRI is (50% to 96%). Evaluation and staging of urinary bladder tumor consist of the numbers, site and pattern of growth of urinary bladder tumors, depth of detrusor muscle invaded by tumor and peri-vesical fat invaded by tumor, and status of lymph node. 5% to 20% of superficial urinary bladder tumors are T1 and T1 is defined as lamina propria invasion without involving detrusor muscle[2,5]. Optimal treatment for T1G3 urinary bladder tumor is with complete resection of urinary bladder tumor through urethra. A bimanual palpation under anesthesia is recommended before and after TURBT to evaluate for any local extension. During TURBT, one should attempt to perform complete resection of urinary bladder tumor, including specimen of deep muscle [5,6]. As it is most common urological malignancy and most of time patients are managed with radical cystectomy and urinary diversion. Diversion in the form of removing urinary bladder is cumbersome and almost all patients do not tolerate it. Also as we go through the literature there is research gap, a few studies are conducted in past on bladder reserving methodology of managing high grade bladder cancer. So in our study, early diagnosis, managing bladder tumor timely and proper follow up decrease muscle invasion. In our study we are sharing our experience of management of high grade non muscle bladder tumor where after radical TUR-BT. BCG was given intravesically then induction and maintenance therapy were installed.[8,9.10]

MATERIAL AND METHODS

This is retrospective study, was conducted at department of urology CMC/SMBBMU Larkana, all the patient were selected from hospital record from July 2016 to June 2022 for period of 06 years. Around 80 patients included in our study group who were treated in our department for management of high grade non-muscle invasive bladder tumor during last 06 years. All those patients who presented with hematuria or ultrasound suggest bladder growth, after taking informed written consent were included in our study and complete blood count, ESR, RBS, serum creatinine, urine culture, cardiac fitness and anesthetic opinion were taken prior to procedure. Patients with uro-sepsis, chronic renal failure or having recent myocardial infarction were excluded from our study. Exclusion criteria were followed strictly to avoid confounding variables, prior TUR-BT bimanual palpation was performed then preceded for TUR-BT using monopolar diathermy, tissue obtained following resection was sent for histopathology. Once biopsy suggested non muscle invasive Transitional cell carcinoma with high grade then intravesically BCG was instilled for induction and maintenance therapy. Post-operative follow up was done with

Diagnostic cystoscopy were done at 3 months, 9 months, 18 months and annually for 05 years and data was collected on study specific proforma.

Data were analyzed according to its type, continuous variables like age were expressed as mean + Standard deviation and discrete variables as percentages like frequencies of high grade tumor and response to BCG and data were analyzed using SPSP 22.0.

RESULTS

In our study patient age range from 55 to 80 years and male to female ratio of 3:1 comprising 60 male and 20 female Fig 02. all the patients who went for TUR-BT and result shown high grade non muscle invasive transitional cell carcinoma, BCG induction and maintenance was given and followed up for 5 years through cystoscopy. Results in our study suggest 70 patients (88.5%) remain disease free, recurrence rate in 5 patients (6.25%) and the progression of disease in 5 patients (6.25%) as shown in Fig No: 02. Some patients developed BCG specific complications that are mentioned in Table No: 01. Disease-specific survival was 93.75% at the follow-up of 5 years. In our study 5 patients developed High grade recurrence or muscle invasive bladder disease they were referred to higher center where Radical cystectomy and urinary diversion were performed.

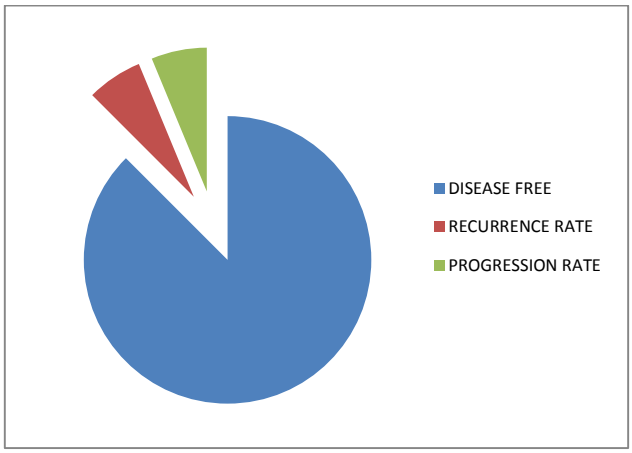

Figure 1: Overall Results

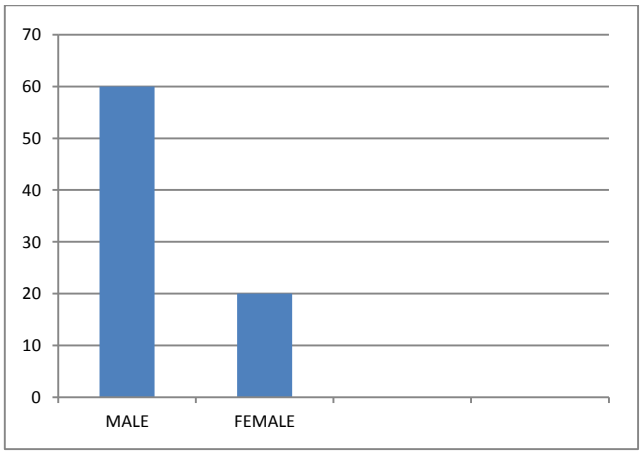

Figure 2: Male to Female Ratio

Table 1: Complications of BCG and Prognosis of T1g3 Tumor

BCG sepsis	1(1.25%)
Recurrence rate	5(6.25%)
Progression	5(6.25%)
Referred for radical cystectomy and diversion	5(6.25%)

DISCUSSION

It has been nearly 100 years since the development of the BCG vaccine was discovered by two scientists Calmette and Guerin more than 100 years ago. BCG activates immune system hence it was used for treatment of cancer. It has many serotypes and in 1976 it was tested intravesically 1st time by Mr Morales for treatment of high grade non-muscle invasive bladder cancer. His results were excellent not only reducing recurrence, slowing progression but also improving disease related overall survival rate in high risk groups.[10]

BCG vaccine is live but weakened form of Mycobacterium Bovis organism which requires intact immune system for its action. It works mostly via two mechanisms: “a direct tumor response” and “immune response.”

BCG attaches to urothelial cells through fibronectin induces cell death either by programmed cell death or by necrosis. Tumor cells activate our own immune system by enhancing major histocompatibility complex-II and intercellular adhesion molecule-1 and are presented to CD4 T cells.[10]

Bladder tumor is further classified into non muscle invasive bladder tumor and invasive bladder tumor accordance to deep muscle involvement.

Non muscle invasive urinary bladder tumors are superficial tumors which do not invade detrusor muscle. Previously it was considered that such tumors do not progress or recur after resection after mitomycin or BCG therapy but long term data from follow-up of these patients revealed that greater than 30% of such cases either progress or have recurrence. In our study mean age 35year + 5.5 SD having male to female ratio 1.33 which is comparable to McHugh LA, Griffiths TR[1].Resection of urinary bladder tumor Initially all these patients were treated with resection of urinary bladder tumor and treated by single shot of mitomycin as well as with induction and maintenance BCG therapy which is comparable to Takashi Saika , Tomoyasu Tsushima et al[10]. Histopathology revealed high grade muscle invasive tumor in all patients. This is lower than study of Sakai I, Miyake H, Harada K et al, which showed 15-years follow up discovered progression of tumor in 53% and required cystectomy in 36% of the patients.

Aims of urinary bladder tumor management are to achieve cancer free survival as well as improve life’s quality. Brausi M, Olaru V. Minerva D[7] reported that upstaging of urinary bladder tumor to muscle invasive or distant metastasis happened in 33% of cases. In our study 5 patients out of 80 developed recurrences of higher stage so referred to higher institute for radical cystectomy and diversion which is comparable to Barentsz JO , Jager G J, J Witjes A et al[9,10].

Results of our study are comparable to Tomas Thiel Charlotta in which 140 patients were enrolled. One patient was excluded, among the 139 patients’ with tumor BCG-treated patients were younger (68.5 vs. 72 years), were staged less as T1 (68 vs. 93%), had more primary CIS (13 vs. 0%) and concomitant CIS (34 vs. 5%), and had more G3 tumors (71 vs. 46%) than non-BCG treated patients. Their study was comparative and most BCG treated patients were young in comparison to our study where we did not keep age as variable. Those patients who did not responded to BCG were treated as immediate cystectomy in our study but in Thomas study risk of recurrence or progression were much higher than our study around 18%**.** In their study within 5 years of clinical follow-up, 29 patients (21%) had died of urothelial carcinoma. Almost all patients who died of bladder cancer, 37 out of 38 patients, had died within 10 years from diagnosis. After 15 years of clinical follow up, 92 patients (66%) had died, of which 38 patients (27%) died of urothelial carcinoma. Stage progression was seen in 50 patients (36%) and recurrence in 76 patients (55%). But in our study recurrence and progression rate was 6.25%, while follow up in our study was 5 years in comparison to Thomas study.[11]

Results of our study are also comparable with Matulay 2021 study, in his study recurrence rate is 8% and progression rate of 9%, while 6.25% in our study which is quite considerable, but

drawback of our study is small sample is comparison to his study which contain 542 patient while our study group include 80 patients.[4]

Our study is also comparable with Farah et al which suggest 70% disease free, recurrence rate of 26.7% and progression rate of 8.3%, while in our study disease free rate of 87% and progression rate of 6.25% which is quite comparable but recurrence rate is quite higher in Farah et al, which is 27% in his study and 6.25% in our study.[12]

In future further studies should be carried out to compare results of disease free, progression and recurrence of disease with more number of patients and longer follow up to validate the results globally for management of carcinoma of bladder.

CONCLUSION

Maintenance therapy with BCG for T1G3 bladder tumors is an effective treatment, having satisfactory results, can be safely used in all age patients and one of the bladder preservation options. But its single centered study; further studies should be conducted so that we can effectively preserve urinary bladder.

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